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SOMMA, MECHANISTIC STUDIES OF MUSCLE AGING IN HUMANS

MUSCLE TRANSCRIPTOMICS INVOLVED IN MITOCHONDRIAL ETS ACTIVITIES ARE ASSOCIATED WITH CARDIORESPIRATORY FITNESS AND PHYSICAL PERFORMANCE IN OLDER ADULTS IN THE STUDY OF MUSCLE, MOBILITY AND AGING (SOMMA)

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Age-related declines in cardiorespiratory fitness and physical performance are major contributors to mobility declines and loss of independence in older adults. Mitochondrial dysfunction has long been implicated in these processes, yet the transcriptomic basis linking mitochondrial bioenergetics to physical performance in older adults remains unclear. We analyzed skeletal muscle mRNA sequencing and detailed phenotyping data from 724 participants in the Study of Muscle, Mobility and Aging, a cohort of community-dwelling adults aged ≥70 years. Seven key measures of physical performance were examined for associations with a biologically curated subset of 225 MitoCarta bioenergetic core genes. These selected genes, derived from both mitochondrial and nuclear genomes, encode proteins involved in electron transport systems, the tricarboxylic acid cycle, and fatty-acid oxidation. Transcriptomic analyses revealed positive associations of MitoCarta bioenergetic core gene expression—particularly genes encoding mitochondrial complexes and TCA cycle enzymes—with multiple physical performance measures. Six genes (SDHAF3, NDUFAF5, NDUFS1, SUCLA2, SDHB, and NDUFAF6) were consistently associated with at least six of the seven physical performance measures. Sex-stratified analyses identified stronger associations of MitoCarta bioenergetic core genes with VO_2peak in women than in men, 85% of protein coding genes from the mitochondrial DNA showing significant sex interactions. Our study suggests that a subset of mitochondrial transcriptomic profiles may serve as molecular drivers of physical performance in late life. These results advance our understanding of the molecular underpinnings of mobility decline in aging and point toward mitochondrial transcriptomic profiles as potential targets for interventions to preserve functional independence with aging.

Keywords: *muscle transcriptome, mitochondrial bioenergetic core genes, electron transport system, physical performance, mobility.*